Cancer Research Center Hotline

Searching for the Causes of Gastric Cancer

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Introduction

It is not highly publicized in the U.S. and elsewhere that gastric cancer has been the second most frequently diagnosed cancer in the world. In a recent report, it was determined that 511,000 men and 287,200 women worldwide would be detected with stomach cancer in a single year, based on data from 23 separate international locations[1]. As a result, gastric cancer is only surpassed by lung cancer in its global impact.

In the United States, there has been a remarkable decline in gastric cancer mortality rates over the past 70 years. In 1930 it was the leading cause of deaths due to cancer in the U.S[2]. Since then, the stomach cancer mortality rates have fallen to about one-fifth of their earlier rates. As a result, gastric cancer is now the eleventh leading cause of cancer deaths in the country. One of the first studies showing gastric cancer mortality trends used data from Hawaii to demonstrate the phenomenon of progressively lower rates among the Japanese who migrated from Japan to Hawaii, indicating that environmental exposures have an important role in the etiology of the disease[3].

Presently, some of the highest gastric cancer incidence rates in the U.S. are found in Hawaii. Persons of Japanese or Native Hawaiian ancestry are particularly susceptible. Among men, the annual incidence rates per 100,000 per year are 21.5 for Japanese, 15.1 for Native Hawaiians, 12.3 for Chinese, 7.8 for Caucasians, and 7.3 for Filipinos, which documents that there is almost a three-fold difference in rates between ethnic groups in Hawaii. For the women, the rates are 10.6 for Japanese, 10.4 for Native Hawaiians, 6.8 for Filipinos, 5.2 for Chinese, and 4.4 for Caucasians[4]. This variation in ethnic-specific rates suggests that either a difference in environmental exposures between the ethnic groups or hereditary factors or both are contributing to the diversity in rates.

Persons Susceptible for Gastric Cancer

With regard to hereditary or genetic factors, familial aggregation studies have usually shown that relatives of gastric cancer patients have a 2-3 fold increase in risk for the same disease compared with relatives of controls[5]. However, these studies do not separate out genetic from environmental factors, because family members tend to share the same environment as well. Besides family members, others who are susceptible to develop gastric cancer include persons with chronic atrophic gastritis (characterized by the loss of gastric glands), persons with intestinal metaplasia of the stomach (defined as the replacement of antral and oxyntic gastric mucosa by glands which have the histological, histochemical, and physiological characteristics of the small intestine), and post-surgical patients after a gastroenterostomy.

Past studies have shown that gastroenterostomy patients are at increased risk for developing gastric cancer many years (usually 20 or more) after surgery. Patients who had undergone the Billroth II procedure, which results in a duodenal stump with a gastrojejunal anastomosis, had a greater risk than those who had the Billroth I procedure, which results in a gastroduodenal anastomosis[6]. It is believed that the regurgitation of alkaline bile and pancreatic juice through the gastrojejunostomy contributes to postoperative gastritis, whereas regurgitation of duodenal contents occurs less often after a gastroduodenostomy[7].

Environmental Factors

The search to identify specific environmental causes of gastric cancer has been a very elusive one[5]. Earlier studies have consistently shown that stomach cancer risk is high among persons in a low socioeconomic status. Social class is related to employment, but occupational studies do not indicate a strong role for any specific occupational gastric carcinogen[8]. It is likely that exposure to ionizing radiation increases the risk for gastric cancer, but relatively few people are exposed to high levels of radiation. Cigarette smokers tend to have a higher risk than nonsmokers, but it is often not related to the amount of cigarettes smoked. Although alcohol intake can result in acute gastritis, the data supporting an association of alcoholic beverages with stomach cancer are weak and inconsistent[5].

Helicobacter pylori, an s-shaped gram-negative microaerophilic bacterium, has been linked to gastric cancer[9,10]. Colonization by the organism has been found in about 30-80% of people in different population groups. The biomechanism by which *H. pylori* infection could lead to gastric cancer is uncertain. The development of cancer has been attributed to increased cellular replication due to the proliferative responses of gastric epithelium, DNA alterations caused by chronic inflammatory reactions, and colonization by enteric bacteria with nitrate reductase activity, which promotes the formation of carcinogenic nitrosamines in an achlorhydric environment. However, because just a small percent of *H. pylori* carriers actually develop stomach cancer, the search continues to identify additional factors to better characterize persons at high risk for this disease.

Diet and Other Factors

Over the years, there has been much interest on the association of gastric cancer with the intake of food groups or nutrients. Because of the inherent difficulties in conducting dietary studies, researchers have not been able to consistently identify specific foods or nutrients that are either harmful for or protective against stomach cancer[5]. A diet high in nitrite-rich foods, salty foods or carbohydrates has been linked to an increased risk, but the findings have not been confirmatory. At the same time, investigators have also shown that a high intake of vegetables, fruits or certain micronutrients decreased gastric cancer risk, but more work needs to be done to substantiate these observations.

In Hawaii, we are conducting a dietary case-control study in which gastric cancer patients and general population controls are compared in their dietary intake and practices to identify specific foods and nutrients that could be associated with this disease. We have an advantage in that a large nutritional data base has been developed over the years at the Cancer Research Center of Hawaii

(CRCH) through the effort of staff nutritionists and dietitians[11]. The resource covers the diets of various ethnic groups participating in our epidemiologic studies. It includes data from over 700 recipes which captures the ethnic foods commonly consumed in Hawaii. The food composition table contains more than 2200 food items and has information on more than 150 nutrients and non-nutrients. With this extensive data base, we hope to be better able to identify specific foods that are linked to stomach cancer.

In addition, a large multiethnic cohort has been identified to study the association of diet and other environmental exposures with cancer[12]. The cohort consists of a total of over 200,000 men and women, of whom more than 100,000 are in Hawaii. They completed a detailed, 26-page questionnaire, which was analyzed with the use of our extensive nutritional data base. Data from the questionnaire will enable us to analyze the effect of different foods, nutrients, and other exposures on gastric cancer risk in a prospective study. Blood and urine samples will also be collected and stored from study participants.

This research resource also provides us with the opportunity to study the interrelationships between dietary and other environmental exposures with polymorphisms in genes that code for enzymes involved in the chemical activation and detoxification of nutrients and carcinogens. These gene markers can be identified from stored white blood cells. For example, the cytochrome P450 enzyme 2E1 metabolically activates a number of low molecular weight potential human carcinogens including benzene and nitrosamines[13]. Nitrosamines and related compounds have been implicated as possible causative agents of gastric cancer[5]. It would be of interest to investigate the association of the *CYP2E1* gene with gastric cancer in relation to dietary, *H. pylori*, and other environmental exposures. Another example is N-acetyltransferase 2 (*NAT2*), a noninducible liver enzyme that deactivates carcinogenic aromatic amines via N-acetylation[14]. Cigarette smokers, who are slow acetylators, have higher levels of 4-aminobiphenyl adducts than rapid acetylators, suggesting a potentiation of effects from cigarette smoking[15]. Because cigarette smokers have been observed to have a high risk for gastric cancer, the association of the *NAT2* polymorphic gene with gastric cancer could also be investigated in relation to smoking and other environmental exposures. We hope that these and other future studies, which will simultaneously combine data on genetic and environmental exposures, will advance our understanding of the specific causes of gastric cancer.

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